DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/10/11 has been entered.

Applicants amendments and arguments and declaration filed 6/10/11 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Previously, applicant elected group 1 (claims 1-40,47-49,53-61,133-136) (11/5/04) and elected a species comprising amino acids LKKTET (2/24/05) for the wound healing polypeptide. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Due to the addition of new claims an additional election of species requirement was sent 1/6/09.

Applicant's election of the following species:

Patient population: skin wound

Further agent: transforming growth factor beta

Further excipient: sterile water

in the reply filed on 2/5/09 is acknowledged.

In the instant case, each of the elected species were found in the prior art. In particular the peptide thymosin beta 4 comprises LKKTET. Any art that was found in the course of searching for the elected species that reads on non-elected species is also cited herein. In accord with section 803.02 of the MPEP the Markush-type claims and the claims to the elected species are rejected and claims to the nonelected species are held withdrawn from consideration. In accord with section 803.02 of the MPEP the search is not extended unnecessarily to cover all species.

Claims 1-236 have been cancelled.

Claims 257,290 are to a species of further excipient other than the elected agents, claims 238-239,243,245-246,249-252,273-274,277,279-280,283-286 is to a patient population other than the elected patient population.

Claims 238-239,243,245-246,249-252,257,273-274,277,279-280,283-286,290 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/5/09.

Claims 237,240-242,244,247-248,253-256,258-272,275-276,278,281-282,287-289,291-294 are under consideration.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 6/10/11 has been considered by the examiner.

Specification

The disclosure is objected to because of the following informalities:

37 CFR 1.821(d) states that: Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In the instant case, applicants have provided a sequence listing. However, each occurrence of the sequences is not preceded by "SEQ ID NO: " as required by 37 CFR 1.821(d). For example see page 10 lines 4,6,20,27; figure 10; figure 11.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The 112 rejections are necessitated by applicants amendments.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 265,292 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 265 and 292 refer to 'substantially free'.

The term "substantially free" in claims 265,292 is a relative term which renders the claim indefinite. The term "substantially free" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is noted that page 18 lines 4-6 of the specification defines substantially pure. However, such phrase is not used in the instant claims. Further, such section defines substantially in terms of substantially. Thus, the definition of substantially pure does not reasonably set forth the scope of the invention.

Although unclear, the claims have been given the broadest reasonable interpretation.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 260-264,267-272,275-276,278,281-282,287-289,291-294 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 260-261 refers to specific effects.

Claims 262-264,267 and dependent claims refer to specific amounts.

Although unclear, the claims have been given the broadest reasonable interpretation.

Lack of Ipsis Verbis Support

The specification is void of any literal support for revascularization of about 2 fold when the administration is for treating any tissue injury.

The specification is void of any literal support for any and all of the ranges of amounts as recited in the claims.

Lack of Implicit or Inherent Support

Section 2163 of the MPEP states: 'While there is no in haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure'.

Applicants argue that support for claims 260-261 is found in Figure 4 and page 31 last paragraph. However, Figure 4 appears to be drawn to wound healing in a rat wound model where the wounds were on the dorsal surface of the rats (see pages 29-30). The instant claims are drawn to administration for a subject in need of tissue repair. There is no indication that the dorsal surface of a rat is the equivalent of any type of tissue. A specific experiment conducted on the dorsal surface is not the equivalent of an experiment on any type of tissue. There is no basis for extrapolating the exact fold increases from an experiment on a dorsal surface to any other type of tissue.

Applicants argue that support for the amounts are found in example 1, figures 2-4, etc. First, it is noted that claims 263-264 refer to 'at least' and claim 267 recites 'greater than' which has no upper limit. Thus even if the specification supports 10% (which is does not) or 6ug it does not necessarily support at least 10% or at least 6 ug. It is noted that example 1 refers to TB4 concentrations of 5ug in 50ul and 60ug in 300ul (page 29 line 10-22). Claim 264,272 reports the amounts as w/v. The University of North Carolina dictionary of units of measurement (retrieved from http://www.unc.edu/~rowlett/units/dictW.html on 7/12/11, 5 pages) teach that w/v (page 4 last entry) is weight by volume and is the mass (in grams) dissolved in or mixed with 100 milliliters of solution. Applicants have disregarded the units in asserting that the specification teach 10% w/v. Applicants have used units of ug/ul while the art teaches appropriate units of g/100ml. 5ug/50ul on a g/100ml basis is (5ug/50ul x2 = 10ug/100ul; 1000ug/mg 1000ul/ml so 10mg/100ml; 1000mg/g so 0.01g/100ml) 0.01% w/v. Thus applicants do not have support for 10% w/v since 0.01% w/v is not the equivalent of nor suggestive of 10% w/v. It is noted that example 1 refers to TB4 concentrations of 5ug in 50ul and 60ug in 300ul (page 29 line 10-22). MPEP 2163.05 III states: With respect to changing numerical range limitations, the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure. In the decision in In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). In the instant case, there is support for 5ug in 50ul and 60ug in 300ul. However, claim 267 for example recites great than 6ug. 5ug in 50 ul is not greater than 6ug. Further, one would not recognize 60ug as representative of any value greater than 6ug. For example, 60ug would not lead one to 1723461731238ug.

Hence, it cannot be said that the specification provides support for claims 260-264,267-272,275-276,278,281-282,287-289,291-294.

Claim Rejections - 35 USC § 102

The 102 rejections are either based on previously recited art or necessitated based on applicants amendments.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 237,240-242,244,247-248,253-256,259-272,275-276,278,281-282,287-289,292-294 are rejected under 35 U.S.C. 102(b) as being anticipated by Turischev (Farmatsiya 'Examining the effects of thymosin on the healing of flat cutaneous wounds in rats' v45 (1996) pages 42-43; first cited 12/30/09) as evidenced by Mann (US 6,030,948).

It is noted that Turischev is in a non-English language. A translated version of the article has been provided and will be relied upon and referenced to herein (Turischev translation of Farmatsiya 'Examining the effects of thymosin on the healing of flat cutaneous wounds in rats' total of 7 pages including the cover page)

Turischev teach the effect of thymosin on the healing of flat skin wounds in rats (title). Turischev teach that Thymosin (5^{th} fraction) was used in the experiments (page 1 last paragraph).

Turischev teach that the composition was administered intraperitoneally or topically to rats with wounds (page 2). Turischev teach that there is clear acceleration of the healing rates and that a dose of 0.8 ug accelerated wound healing for a particular administration (page 3). Turischev teach an index of completion of the healing and report specific values for the administration modes (pages 2-4) and refer to different stages of healing (page 2) thus there is a reasonable basis that an effective amount was used. Turischev does not recite the components of thymosin 5^{th} fraction. Mann teach (column 4 lines 8-53) that thymosin fraction 5 contains thymosin beta4 (column 4 line 31) and thymosin alpha 1 (column 4 line 26). Mann (US 6030948) teach thymosin beta 4 as a major component of TF5 (column 4 lines 43-53) and that TF5 is essentially free of lipids and carbohydrates (column 4 lines 18-19). Mann is cited as a universal fact to reveal the components of thymosin fraction 5 and thus need not be prior art (MPEP 2124).

Since Turischev teach rats with skin wounds and intraperitoneally and topical administration of TF5 which was in physiological solution (see page 2 line 4-5) the active steps of claims 237,240-242,244,248,253-256,259-272,275-276,278,281-282,287-289,292-294 are met. Turischev teach that Thymosin (5^{th} fraction) was used in the experiments (page 1 last paragraph) and Mann states that such fraction contains thymosin beta 4 and thymosin alpha 1 (see applicants original claim 12 and admission on page 21 lines 4-5 of the reply dated 3/30/10, and see page 11 of specification of the current invention) the composition limitations of claims 254 are met.

It is noted that certain claims recite properties – re-epithealization, revitalize etc. Since Turischev teach the elected agent (i.e. thymosin beta 4) the claim limitations are met (see also MPEP 2112.01) absence evidence to the contrary. With respect to amounts, Turischev provide a

reference about the method of preparation (see reference 5). However, the office has no facility to test such fraction as described by Turischev. Thus, the claim limitations are met absence evidence to the contrary.

Although unclear, the claims have been given the broadest reasonable interpretation.

Response to Arguments 102

Applicants argue (pages 10-26) that the claims have been amended and that the instant claim limitations have not been met.

Applicants argue that Turischev teach away from topical use of TF5 and teach that topical administration of TF5 decreased wound healing and was detrimental and causes negative effects and is ineffective and that Turischev did not disclose tissue repair and that Turischev disclosed ineffective doses.

Applicants assert (page 13) that TF5 contains 0.45% thymosin beta 4 and refer to Low et al (page 17).

Applicants assert (page 14) that 0.2 ug/g diluted in 0.5ml is 0.04% w/v.

Applicants argue (page 15) that Turischev has not formed a nexus with the requirements of the presently claimed claims and argue that the specification talks about scar tissue.

Applicants argue that Turischev does not teach tissue repair and revitalization.

Applicants argue that the declaration asserts that the Turischev reference demonstrates that administration was unpredictable. The declaration states that the results were confounding and one would have been unable to extract suggestions and one would have been dissuaded from topical administration or intraperitoneally at a dose other than 0.8 ug/g.

Applicants argue that the declaration asserts that it is not known which component of TF5 can be attributed to the outcome.

Applicants argue that the declaration asserts that there is a technical difference between wound healing and tissue repair and that references about corneal wound healing show a lack of suppuration.

Applicants argue that the declaration asserts that compared to a control the healing was not significantly accelerated.

Applicant's arguments and declaration filed 6/10/11 have been fully considered but they are not persuasive.

Although Applicants argue (pages 10-26) that the claims have been amended and that the instant claim limitations have not been met, the rejections as set forth above discuss which of the amended claims are rejected and explains how the claim limitations are met.

Although Applicants argue that Turischev teach away from topical use of TF5 and teach that topical administration of TF5 decreased wound healing and was detrimental and causes negative effects and is ineffective and that Turischev did not disclose tissue repair and that Turischev disclosed ineffective doses, MPEP 2131.05 states:

"Arguments that the alleged anticipatory prior art is nonanalogous art' or teaches away from the invention' or is not recognized as solving the problem solved by the claimed invention, [are] not germane' to a rejection under section 102." Twin Disc, Inc. v. United States, 231 USPQ 417, 424 (Cl. Ct. 1986) (quoting In re Self, 671 F.2d 1344, 213 USPQ 1, 7 (CCPA 1982)). See also State Contracting & Eng ' g Corp. v. Condotte America, Inc., 346 F.3d 1057, 1068, 68 USPQ2d 1481, 1488 (Fed. Cir.

2003) (The question of whether a reference is analogous art is not relevant to whether that reference anticipates. A reference may be directed to an entirely different problem than the one addressed by the inventor, or may be from an entirely different field of endeavor than that of the claimed invention, yet the reference is still anticipatory if it explicitly or inherently discloses every limitation recited in the claims.).

A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. **The question whether a reference "teaches away" from the invention is inapplicable to an anticipation analysis.** Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The prior art was held to anticipate the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). >See Upsher-Smith Labs. v. Pamlab, LLC, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(claimed composition that expressly excluded an ingredient held anticipated by reference composition that optionally included that same ingredient);< see also Atlas Powder Co. v. IRECO, Inc., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999) (Claimed composition was anticipated by prior art reference that inherently met claim limitation of "sufficient aeration" even though reference taught away from air entrapment or purposeful aeration.). (emphasis added)

In the instant case, the prior art teach the steps as claimed thus the reference is anticipatory. Further, although applicants assert that there is 'decreased wound healing', it is noted that the claims refer to 'effective to repair'. It is noted that the rate or time of repair is not recited in the

instant claims. Thus, whether or not repair is slow or fast is not the relevant issue. Turischev teach that the wounds go through different stages of healing (page 2 last complete paragraph). For the topical administrations the index of completion of the healing process is evidence of repair (page 4 , ICHP is 0.66) thus there necessarily is wound healing and growth (see index of completion as defined on pages 2-3 of Turischev). Although certain administrations may result in 'faster' rates or may differ compared to a control, there are no rates or times or controls recited in claims 237,267. Although applicants assert that the administration is 'ineffective' the index of completion of the healing process is evidence that repair is taking place, thus applicants assertion is unsubstantiated. Applicants refer to 'slower healing' and 'slower contraction' (page 20 first complete paragraph) which is further evidence that healing and contraction occurred. To reiterate, the time or healing or contraction does not take away from the fact that healing and contraction occurred.

Although Applicants assert (page 13) that TF5 contains 0.45% thymosin beta 4 and refer to Low et al (page 17), the facts of the case show that Turischev use T (5^{th} fraction) (see page 1 last paragraph) and Turischev even goes so far as to provide a reference about the method of preparation (see reference 5). The relevant issue is how much thymosin beta 4 is in the fraction used by Turischev. Applicants refer to Low. However, Low does not answer the question of how much thymosin beta 4 is in the fraction as used by Turischev. The thymosin of Turischev is from a whale and the thymosin of Low is from a calf. There is no evidence that the different species would have the same thymosin beta 4 levels. Importantly, Low is reporting **a yield** of thymosin beta 4 from fraction 5, not how much thymosin beta 4 is in fraction 5. Low does not define yield. However, the art recognizes that yield is a function of the purification steps. Since a yield is a

function of the purification steps it is not the equivalent of a concentration. For example, product is often lost at various stages of purification. The biotechnology project discuss percent yield (The biotechnology project retrieved from http://biotech.matcmadison.edu/resources/proteins/labManual/chapter_3/sample3_6.htm 2 pages retrieved on 7/18/11). Further, Rutgers university (Rutgers university retrieved from http://aesop.rutgers.edu/~dbm/Protein%20purif%20I.html retrieved on 7/18/11 8 pages) teach that: "Yield is total units at a given step divided by total units in the crude extract; it decreases through the purification, and in a long purification the final yield may be only a few per cent" (see page 3). Thus there is absolutely no basis to equate a yield with a concentration. It is noted that Turischev even goes so far as to provide a reference about the method of preparation (see reference 5). However, the office has no facility to test such fraction as described by Turischev. In the instant case, Mann (US 6030948) teach thymosin beta 4 as a major component of TF5 (column 4 lines 43-53) and that TF5 is essentially free of lipids and carbohydrates (column 4 lines 18-19). Further, Nayar ('Structure and function of thymosin beta 4' retrieved from http://chemistry.cua.edu/res/docs/grad/nayar-comp.doc on 7/18/11 22 pages) teach thymosin beta4 as the most abundant of beta thymosins (page 3) and show (figure 1) that thymosin beta 4 appears much darker than any of the alpha or beta thymosins (see figure 1 and page 3) thus there is a reasonable basis that thymosin beta 4 is present at more than 0.45% in a typical TF5 preparation.

Although Applicants assert (page 14) that 0.2 ug/g diluted in 0.5ml is 0.04% w/v, it is unclear how applicants have derived such numbers. 0.2ug/g means that 0.2ug per g of subject. If the subject is 1g then there is 0.2ug. If the subject is 1000g then there is 200ug. Since 0.2ug/g is

variable there is no basis to calculate a single value of 0.04% w/v. In other words 0.2ug/0.5ml and 200ug/0.5ml can not both be 0.04% w/v. It is noted that applicants assert that support for 10% w/v is found in the specification. It is noted that example 1 refers to TB4 concentrations of 5ug in 50ul and 60ug in 300ul (page 29 line 10-22). As claimed the amounts are reported as w/v. The University of North Carolina dictionary of units of measurement (retrieved from http://www.unc.edu/~rowlett/units/dictW.html on 7/12/11, 5 pages) teach that w/v (page 4 last entry) is weight by volume and is the mass (in grams) dissolved in or mixed with 100 milliliters of solution. Applicants have disregarded the units in asserting that the specification teach 10% w/v. Applicants have used units of ug/ul while the art teaches appropriate units of g/100ml. 5ug/50ul on a g/100ml basis is (5ug/50ul x2 = 10ug/100ul; 1000ug/mg 1000ul/ml so 10mg/100ml; 1000mg/g so 0.01g/100ml) 0.01% w/v. Thus applicants do not have support for 10% w/v since 0.01% w/v is not the equivalent of nor suggestive of 10% w/v.

Although Applicants argue (page 15) that Turischev has not formed a nexus with the requirements of the presently claimed claims and argue that the specification talks about scar tissue, it is noted that the claims are not drawn to methods of forming a nexus. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., forming a nexus) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Although Applicants argue that Turischev does not teach tissue repair and revitalization, MPEP 2112.01 states that: Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). In the instant case Turischev teach compositions containing the agent as claimed. There is no basis for asserting that the properties of thymosin beta4 are not present in a composition of thymosin beta4. Further, Turischev teach that the wounds go through different stages of healing (page 2 last complete paragraph). For the topical administrations the index of completion of the healing process is evidence of repair (page 4 , ICHP is 0.66) thus there necessarily is wound healing and growth (see index of completion as defined on pages 2-3 of Turischev).

Although Applicants argue that the declaration asserts that the Turischev reference demonstrates that administration was unpredictable, as cited above (MPEP 2131.05): **A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. The question whether a reference "teaches away" from the invention is inapplicable to an anticipation analysis.** Thus, whether or not the reference itself or a declaration by H. Paul Ehrlich is disparaging does not make a reference any less anticipatory. The issue in a 102 rejection is not extracting suggestions. As discussed above certain claims are anticipated because they are taught by the prior art.

Although Applicants argue that the declaration asserts that it is not known which component of TF5 can be attributed to the outcome, the fact remains that the prior art teach a composition containing the claimed component. The instant claims are not drawn to methods of

determining which agent can be attributed to the outcome. The claims require administration of TB4 which is taught by the prior art.

Although Applicants argue that the declaration asserts that there is a technical difference between wound healing and tissue repair and that references about corneal wound healing show a lack of suppuration, instant claims 237 and 267 require a subject in need of tissue repair which is taught by the prior art. Since the prior art teach administration of the claimed agent to such patient populations there is a reasonable basis that the claim limitations are met absence evidence to the contrary (see MPEP 2112.01). It is unclear how references about corneal wound healing are evidence that the prior art does not teach the instant claim limitations. Instant claims 237 and 267 do not refer to a time period for repair nor due the claims refer to a lack of suppuration. As noted in a previous office action (6/9/10), the dictionary (The Free online dictionary (entry for healing) http://www.thefreedictionary.com/healing accessed on 5/26/10 4 pages) expressly defines healing to be repair (page 1, heal 2nd definition). Applicants assertion is contradictory to the term definition.

Although Applicants argue that the declaration asserts that compared to a control the healing was not significantly accelerated, claims 237 and 267 do not refer to methods of administration to a control. It is noted that the rate or time of repair is not recited in the instant claims. Thus, whether or not repair is slow or fast is not the relevant issue. Turischev teach that the wounds go through different stages of healing (page 2 last complete paragraph). For the topical administrations the index of completion of the healing process is evidence of repair (page 4 , ICHP is 0.66) thus there necessarily is wound healing and growth (see index of completion as defined on pages 2-3 of Turischev).

In summary, the declaration under 37 CFR 1.132 filed 6/10/11 is insufficient to overcome the rejection of claims as set forth above. As stated in MPEP 2131.04, secondary considerations are irrelevant to a 102 rejection. In the instant case, arguments that the reference teaches away are irrelevant to the 102 rejection. Further, arguments about the amounts (equating a yield and a concentration; converting to w/v) are inconsistent with the prior art methodology. Thus applicants assertions and opinions are not adequate to show that the prior art does not teach the limitations recited in the instant claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 267-268,270,275,278,282,287-289,292-294 are rejected under 35 U.S.C. 102(b) as being anticipated by Goldstein et al (US 5,578,570) as evidenced by Lai (US 5,358,703).

Goldstein teach treating septic shock by administering thymosin beta 4 (abstract). Goldstein teach administration of thymosin beta4 (claim 1) to humans (claim 2) in a dose of 0.4-4 mg/kg (claim 4) where the agent is administered intravenously (claim 6) thus meeting the active step of claims 267-268,270,275,278,282,287-289,292-294. Lai teach (column 1 lines 41-45) that septic shock is manifested by tissue damage. Lai is cited as evidence that those with

septic shock are in need of tissue repair. Thus Goldstein teach the patient population of claims 267-268,270,275,278,282,287-289,292-294.

Although unclear, the claims have been given the broadest reasonable interpretation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 237,240-242,244,247-248,253-256,258-272,275-276,278,281-282,287-289,291-294 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldstein et al (US 5,578,570) and Lai (US 5,358,703) and Palladino et al (US 5,055,447).

Goldstein teach treating septic shock by administering thymosin beta 4 (abstract).

Goldstein does not reduce to practice using topical administrations. Goldstein does not teach in a single embodiment the use of transforming growth factor beta.

Goldstein teach administration of thymosin beta4 (claim 1) to humans (claim 2) in a dose of 0.4-4 mg/kg (claim 4) where the agent is administered intravenously (claim 6) thus meeting the active step of claims 267-268,270,275,278,282,287-289,292-294. Goldstein teach various administration modes including topical (column 2 line 53, column 3 lines 33-38) and suggest compositions containing sterile water (column 4 line 4) and the use of gels (column 3 line 40) thus one would be motivated to use such compositions thus meeting the limitations as recited in claims 237,253,255-256 for example. Goldstein teach the use of synthetic Tbeta4 (column 4 lines 61-64) thus one would be motivated to use such form as recited in claim 244 for example. Golsdtein expressly teach dosages of 0.4 - 4 mg per kg of body weight (claim 3) (for an average 70 kg person the dose is 28-280 mg). Further, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g.dosages), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2144.05).

Lai teach (column 1 lines 41-45) that septic shock is manifested by tissue damage. Lai is cited to show that those with septic shock are in need of tissue repair. Thus one would be motivated to treat the patient population of claims 267-268,270,275,278,282,287-289,292-294.

Goldstein teach treating septic shock. In order to address the problem one would be motivated to use other known techniques of treating septic shock. Pallidino teach treating septic shock by administering transforming growth factor beta (claim 1). Thus one would be motivated to administer such agent to those with septic shock as recited in claims 258 for example. Further, Pallidino teach that those with septic shock ordinarily experiences skin lesions (column 5 lines 45-47). Thus one would be motivated to treat the skin lesions thus meeting the limitations recited in the instant claims (for example claim 240).

In the instant case, one would be motivated to address the problem of treating septic shock as set forth by Goldstein by using the methods expressly suggested by Goldstein. Since Goldstein expressly claim methods of treating one would have a reasonable expectation of success. Since Pallidino also teach methods of treating septic shock one would be motivated to use such teachings to address the problem of treating septic shock with a reasonable expectation of success.

It is noted that certain claims refer to properties (revitalize, increase re-epithelialization). Since Goldstein teach the claimed agent at the claimed amounts (compare claim 270) there is a reasonable basis that all claim limitations are met absence evidence to the contrary.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Although unclear, the claims have been given the broadest reasonable interpretation.

Double Patenting

It is noted that application 12938228 is a divisional of copending US Serial No. 09/772,445. The restriction requirement for 09/772,445 was mailed 10/5/04. The instant claims of 12938228 are not consonant with the restriction requirement of 10/5/04. Thus in accord with MPEP 804.01(b) the prohibition against double patenting does not apply to US Serial No. 09/772,445.

Claims were previously rejected based on double patenting. The rejections have been updated to correspond to the instant claims.

The terminal disclaimer filed on 9/17/08 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US 7,268,118 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The terminal disclaimer filed on 9/17/08 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on 11/284,430 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 237,240-242,244,247-248,253-256,258-266 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 48-73 of copending Application No. 11/284,408 ('408). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '408 application teaches methods of administering compositions to skin comprising thymosin beta four (for example, claim 48), transforming growth factor (claim 53), and a vehicle (claim 48) for topical treatment (for example, claim 52) in the form of a lotion (claim 72). '408 teach the administration to improve skin appearance and is applied to thinning skin (claim 53,70) and for wound repair (title) thus one would be motivated to administer to those of the instant claims. Taken together, the limitations of claims set forth above are met.

It is noted that certain claims recite properties. Since '408 teach the elected agent (i.e. thymosin beta 4) which is recited in the claims the claim limitations are met (see also MPEP 2112.01). It is noted that the claims refer to effective amounts. Since '408 expressly teach amounts (claim 48-49) and methods for improving the appearance of the skin (claim 53) the amounts are effective.

Although unclear, the claims have been given the broadest reasonable interpretation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 237,240-242,244,247-248,253-256,258-272,275-276,278,281-282,287-289,291-294 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-23,26 of copending Application No. 11/917,869 ('869). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '869 application teaches methods of administering compositions to the skin comprising thymosin beta four isoform or LKKTET (for example, claim 13,21), and a stimulating agent (claim 13), and a carrier (claim 17), and teach the composition as a lotion (claim 20), and teach specific doses (claim 23). The method is for treating tissue and injured or damaged skin thus one would be motivated to treat the patients as in the instant claims.

It is noted that certain claims recite properties. Since '869 teach the elected agent (i.e. thymosin beta 4) which is recited in the claims the claim limitations are met (see also MPEP 2112.01).

Although unclear, the claims have been given the broadest reasonable interpretation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 237,240-242,244,247-248,253-256,258-272,275-276,278,281-282,287-289,291-294 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting

as being unpatentable over claims 21-32 of copending Application No. 11/715,997 ('997). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '997 application teaches methods of administering compositions to the skin comprising thymosin beta four or LKKTET (for example, claim 21), and specific doses (claim 27), and as a lotion (claim 22), and with a carrier (claim 23). The method is for treating tissue and injured or damaged skin thus one would be motivated to treat the patients as in the instant claims.

It is noted that certain claims recite properties. Since '997 teach the elected agent (i.e. thymosin beta 4) which is recited in the claims the claim limitations are met (see also MPEP 2112.01).

Although unclear, the claims have been given the broadest reasonable interpretation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 237,240-242,244,247-248,253-256,258-272,275-276,278,281-282,287-289,291-294 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25 of copending Application No. 12/444,331 ('331). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '331 application teaches methods of administering compositions to the skin comprising thymosin beta four or LKKTET (for example, claim 1), and specific doses (claim 7), and lotions as a form (claim 11).The method is for treating tissue and injured or damaged skin thus one would be motivated to treat the patients as in the instant claims.

It is noted that certain claims recite properties. Since '331 teach the elected agent (i.e. thymosin beta 4) which is recited in the claims the claim limitations are met (see also MPEP 2112.01).

Although unclear, the claims have been given the broadest reasonable interpretation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 267-268,270,275,278,282,287-289,292-294 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,578,570 (Goldstein) as evidenced by Lai (US 5,358,703).

Goldstein teach treating septic shock by administering thymosin beta 4 (abstract). Goldstein teach administration of thymosin beta4 (claim 1) to humans (claim 2) in a dose of 0.4-4 mg/kg (claim 4) where the agent is administered intravenously (claim 6) thus meeting the active step of claims 267-268,270,275,278,282,287-289,292-294. Lai teach (column 1 lines 41-45) that septic shock is manifested by tissue damage. Lai is cited as evidence that those with septic shock are in need of tissue repair. Thus Goldstein teach the patient population of claims 267-268,270,275,278,282,287-289,292-294.

Although unclear, the claims have been given the broadest reasonable interpretation.

Claims 237,240-242,244,247-248,253-256,258-272,275-276,278,281-282,287-289,291-294 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-25 of copending Application No. 12/444,331 ('331).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '331 application teaches methods of administering compositions to the skin comprising thymosin beta four or LKKTET (for example, claim 1), and specific doses (claim 7), and lotions as a form (claim 11).The method is for treating tissue and injured or damaged skin thus one would be motivated to treat the patients as in the instant claims.

It is noted that certain claims recite properties. Since '331 teach the elected agent (i.e. thymosin beta 4) which is recited in the claims the claim limitations are met (see also MPEP 2112.01).

Although unclear, the claims have been given the broadest reasonable interpretation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 267-268,270-272,275,278,282,287-289,292-294 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21 of copending Application No. 12/938,228 ('228). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '228 application teaches methods of administering compositions to injured tissue comprising thymosin beta (for example, claim 1) by direct administration (claim 6).

It is noted that certain claims recite properties. Since '228 teach the elected agent (i.e. thymosin beta 4) which is recited in the claims the claim limitations are met (see also MPEP 2112.01).

Although unclear, the claims have been given the broadest reasonable interpretation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 267-268,270-272,275,278,282,287-289,292-294 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 12/160,720 (720). Although the conflicting claims are not identical, they are not patentably distinct from each other.

720 teach administration of compositions comprising thymosin beta 4 (claim 1), systemically and directly to coronary tissue (claims 3-4) for treating tissue damage in specific patients (claim 10,18) in specific amounts (claim 25).

It is noted that certain claims recite properties. Since '228 teach the elected agent (i.e. thymosin beta 4) which is recited in the claims the claim limitations are met (see also MPEP 2112.01).

Although unclear, the claims have been given the broadest reasonable interpretation.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims are directed to an invention not patentably distinct from claims of commonly assigned applications/patents as discussed above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300).

Commonly assigned applicants/patents discussed above, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Response to Arguments double patenting

Applicants request that the rejections be held in abeyance

Applicant's arguments filed 6/10/11 have been fully considered but they are not persuasive.

Although Applicants request that the rejection be held in abeyance, the rejections listed above remain of record. The rejections have not been overcome.

Prior art of record

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Malinda et al (Faseb Journal 1997 cited in IDS 5/25/01). Malinda teach that TB4 is important in angiogenesis and that the formation of blood vessels is an important part of wound healing (page 480). Malinda teach that others report that TB4 could play a major role in would healing (page 480). Malinda recognizes the use of in vivo experiments (abstract).

Baumann et al 1997 (from 'Thymic peptides in preclinical and clinical medicine: an update:proceedings of the 2nd international thymus symposium' editor HR Maurer, pages 13-17; cited previously). Baumann (Table II page 21) also teach that TB4 leads to an increase in wound healing in vitro.

Biotech Patent News (Dec 1 1997 1 page, cited previously). Biotech Patent News teach that investigators will use thymosin beta 4 (last paragraph) in a wound healing study.

Goldstein et al (cited 2/21/08 ref 14). Goldstein teach tissue regeneration via thymosin (title).

Bilton (WO 84/02274) - Bilton teach compositions for wound healing (title) including those that include thymus concentrate (claim 1, example 1).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ronald T Niebauer/
Examiner, Art Unit 1654

/CECILIA J TSANG/
Supervisory Patent Examiner, Art Unit 1654